Lack of Durable Improvements in β-Cell Function Following Withdrawal of Pharmacological Interventions in Adults With Impaired Glucose Tolerance or Recently Diagnosed Type 2 Diabetes

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OBJECTIVE

The Restoring Insulin Secretion (RISE) Adult Medication Study compared pharmacological approaches targeted to improve β-cell function in individuals with impaired glucose tolerance (IGT) or treatment-naive type 2 diabetes of <12 months duration.

RESEARCH DESIGN AND METHODS

A total of 267 adults with IGT (*n* = 197, 74%) or recently diagnosed type 2 diabetes (*n* = 70, 26%) were studied. Participants were randomized to receive 12 months of metformin alone, 3 months of insulin glargine with a target fasting glucose <5 mmol/L followed by 9 months of metformin, 12 months of liraglutide combined with metformin, or 12 months of placebo. β-Cell function was assessed using hyperglycemic clamps at baseline, 12 months (on treatment), and 15 months (3 months off treatment). The primary outcome was β-cell function at 15 months compared with baseline.

RESULTS

All three active treatments produced on-treatment reductions in weight and improvements in HbA_{1c} compared with placebo; the greatest reductions were seen in the liraglutide plus metformin group. At 12 months, glucose-stimulated C-peptide responses improved in the three active treatment groups and were greatest in the liraglutide plus metformin group, but the arginine-stimulated incremental C-peptide response was reduced in the liraglutide plus metformin group. Despite on-treatment benefits, 3 months after treatment withdrawal there were no sustained improvements in β-cell function in any treatment group.

CONCLUSIONS

In adults with IGT or recently diagnosed type 2 diabetes, interventions that improved β-cell function during active treatment failed to produce persistent benefits after treatment withdrawal. These observations suggest that continued intervention may be required to alter the progressive β-cell dysfunction in IGT or early type 2 diabetes.

PATHOPHYSIOLOGY/COMPLICATIONS

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**A complete list of the RISE Consortium Investigators can be found in the Supplementary Data.*

This article is featured in a podcast available at http://www.diabetesjournals.org/content/diabetes-core-update-podcasts.

Progression from prediabetes to type 2 diabetes is driven by ongoing worsening of β-cell secretory function in the setting of insulin resistance (1,2). Similarly, in established diabetes, progressive loss of glycemic control arises from ongoing deterioration of β-cell function (2). Prior research has demonstrated that interventions targeting improvements in β-cell function and/or insulin sensitivity can be effective in slowing or reversing this progressive loss of glycemic control. Such approaches include reducing insulin secretory demand by improving insulin sensitivity through weight loss, metformin, or peroxisome proliferator–activated receptor gamma agonists (3–10); inducing β-cell rest using exogenous insulin (11–13); or augmenting β-cell function to overcome functional deficits using glucagon-like peptide 1 (GLP-1) agonists (14–16). These interventions exhibit ongoing efficacy for ameliorating hyperglycemia during treatment, but only lifestyle interventions (3,5,17–19) and treatment with thiazolidinediones (9,10,20,21) have been show to affect the natural history of progressive β-cell dysfunction. One approach to evaluate effects on the natural history is to examine whether treatment effects persist following treatment withdrawal. Persisting effects on β-cell function post-withdrawal were seen in adults with type 2 diabetes treated with intensive insulin therapy using multiple daily injections or subcutaneous continuous insulin infusion (11,12) and in adults with prediabetes treated with pioglitazone (10,22), but not in adults with diabetes treated with exenatide or liraglutide (14–16).

Metformin is currently the preferred pharmacological treatment for diabetes prevention (23). The durability of efficacy following metformin withdrawal has not been systematically evaluated for longer than 2 weeks (24). It is therefore important to include metformin in a study of treatment durability and to study a longer withdrawal interval.

The Restoring Insulin Secretion (RISE) Adult Medication Study was a proof-of-principle trial to compare approaches to improving β-cell function in adults with impaired glucose tolerance (IGT) and recently diagnosed type 2 diabetes. Owing to failed interventions in established diabetes, we focused on individuals earlier in the development of dysglycemia. The study used a four-arm randomized approach comparing insulin glargine for 3 months followed by metformin for 9 months (G/M) or liraglutide combined with metformin (L+M) for 12 months against 12 months of blinded metformin alone or matched placebo. β-cell function was quantified using hyperglycemic clamps at baseline prior to randomization, at the end of 12 months (M12) of active therapy, and at 15 months (M15), i.e., 3 months following therapy withdrawal, to assess on-treatment effects and effects following withdrawal of therapy. The primary question was the durability of the treatment effect post-withdrawal, testing the hypothesis that G/M or L+M would be superior to metformin alone and to placebo in sustaining improvements in clamp-measured β-cell function at M15 compared with baseline.

RESEARCH DESIGN AND METHODS

Study Protocol

The RISE Adult Medication Study was a three-center, randomized, partially blinded clinical trial funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The rationale and methods have been described in detail (25,26), and the study protocol is available online at https://rise.bsc.gwu.edu/web/rise/collaborators. Each center's institutional review board approved the protocol. Written informed consent was obtained, consistent with the Declaration of Helsinki and each center's institutional review board guidelines.

Participants

Enrollment occurred between July 2013 and October 2017. Eligibility criteria included age 20–65 years and BMI $\geq$25 and $<$50 kg/m^2 ($\geq$23 kg/m^2 for Asian Americans), with IGT or drug-naive physician-diagnosed type 2 diabetes of $<$12 months duration. Screening included a 2-h 75-g oral glucose tolerance test (OGTT). Eligibility required fasting glucose 5.3–6.9 mmol/L, OGTT 2-h glucose $\geq$7.8 mmol/L, and HbA_{1c} $\leq$64 mmol/mol (7.0%). At screening, all participants were provided with routine recommendations for weight loss and exercise consistent with the U.S. Diabetes Prevention Program (DPP) recommendations, as well as standard diabetes education. These recommendations were reinforced at ongoing quarterly visits.

All screen-eligible individuals participated in a placebo run-in period. Final study eligibility required $\geq$80% adherence to 3 weeks of twice-daily oral placebo tablets and once-daily injection placebo, and full attendance at scheduled run-in visits. Eligible participants underwent baseline measurements including the hyperglycemic clamp, followed by random 1:4 treatment assignment stratified by study site and by screening diabetes status. Progress of participants through the study is summarized in the Consolidated Standards of Reporting Trials (CONSORT) diagram (Supplementary Fig. 1).

Interventions

Participants randomized to 12 months of metformin alone or placebo received double-blinded tablets. Medication titration occurred over 4 weeks, starting with one tablet daily (500 mg metformin or placebo), to a maximum dose of two tablets twice daily. Participants experiencing intolerance returned to the highest previously tolerated dose.

The G/M group received 3 months of insulin glargine titrated at least twice weekly using a predefined algorithm (Appendix 2 in Supplementary Data) to achieve a fasting glucose of 4.4–5.0 mmol/L based on daily self-monitored blood glucose, immediately followed by 9 months of metformin (unblinded, titrated to a goal of 1,000 mg twice daily).

The L+M group received 12 months of liraglutide combined with metformin. Liraglutide was started first, with weekly titration from 0.6 to 1.2 to 1.8 mg daily in the morning as tolerated. After establishing a stable, tolerated liraglutide dose, metformin (unblinded) was added and titrated to a goal of 1,000 mg twice daily. When required because of adverse effects, metformin was reduced before reductions in liraglutide exposure were pursued.

Participants received active intervention for a total of 12 months. Randomized interventions were then withdrawn. Study measurements were repeated 3 months after medication withdrawal to address durability.

Medication adherence (returned pill counts and injectable pen residual volume) and adverse effects were assessed at all study visits. Hypoglycemia, hyperglycemia, and acute metabolic decompensation were systematically assessed

at each visit (Appendix 3 in Supplementary Data). Safety was monitored by an independent Data and Safety Monitoring Board.

Procedures and Calculations

Hyperglycemic Clamp

A two-step hyperglycemic clamp (11.1 mmol/L, then >25 mmol/L plus arginine) was performed at baseline, M12, and M15 as described previously (27). Participants taking metformin or placebo took the last tablet the evening prior to the hyperglycemic clamp; liraglutide was last taken the morning of the M12 measurement.

The hyperglycemic clamp was used to simultaneously quantify insulin sensitivity (quantified as M/I, defined below) and three β-cell response measures: *1*) steady-state (second-phase) C-peptide (SSCP), *2*) acute C-peptide response to arginine at maximal glycemic potentiation ($ACPR_{max}$), and *3*) acute (first-phase) C-peptide response to glucose ($ACPR_g$).

M/I was calculated as the mean glucose infusion rate (M) at 100, 110, and 120 min of the clamp divided by the corresponding mean steady-state plasma insulin concentration (I) (27). Mean SSCP concentrations were calculated using samples obtained at 100, 110, and 120 min. $ACPR_{max}$ was calculated as the mean incremental C-peptide above concentrations achieved with hyperglycemia prior to the arginine bolus. $ACPR_g$ was calculated as the mean incremental C-peptide above baseline for the first 10 min after the glucose bolus. β-cell function was evaluated using C-peptide response measures paired with concurrently measured insulin sensitivity (27). The approach to statistical analysis using these paired responses is outlined in the Statistical Analysis Plan (Appendix 4 in Supplementary Data).

HbA_{1c} Monitoring

HbA_{1c} was measured quarterly to assess glycemic responses and monitor for glycemic worsening.

Assays

Laboratory assessments were performed in a central laboratory at the University of Washington, as described previously (25,27). With a focus on measurements related to the primary outcomes, glucose was measured using the glucose hexokinase method on a Roche c501 autoanalyzer (Roche Diagnostics, Indianapolis, IN) and C-peptide and insulin by two-site immunoenzymometric assays performed on a Tosoh 2000 autoanalyzer (Tosoh Biosciences, Inc., South San Francisco, CA). Interassay coefficients of variation on quality control samples with low, medium, medium-high, and high concentrations were ≤2.0% for glucose, ≤4.3% for C-peptide, and ≤3.5% for insulin.

Statistics

Data were collected centrally, and analyses were performed according to a prespecified Statistical Analysis Plan (Appendix 4 in Supplementary Data). Two measures of β-cell function at M15 served as co–primary outcomes (clamp-derived SSCP and $ACPR_{max}$), each evaluated jointly with insulin sensitivity (quantified as M/I), adjusted for baseline. Joint models for β-cell response and insulin sensitivity were fit simultaneously using seemingly unrelated regression techniques (28–30), which provided a test of the treatment arm differences in the concurrent measures of β-cell response and insulin sensitivity. The two primary outcomes were analyzed separately, with a total type I error probability of 0.05 for each. All models used natural logarithmically transformed insulin sensitivity (M/I) and β-cell response variables owing to the skewed distribution of these data. $ACPR_g$ was evaluated as a prespecified secondary outcome. Prior to taking logs, a constant of 1.06 was added to the $ACPR_g$ because of negative values in this β-cell response variable. The same analytical methods were used to compare treatment groups at M12 as prespecified secondary analyses.

To evaluate changes within each treatment arm over time, the Hotelling T^2 method was used to simultaneously test changes in β-cell responses and insulin sensitivity (31). Additional secondary analyses compared means across treatment arms at specific time points using ANOVA, and paired *t* tests were used to evaluate changes within each treatment arm over time.

Based on available unpublished data, sample size was calculated using a two-sided significance level of 0.05 for comparisons of a given pair of treatment arms and a conservative correlation of at least 0.57 between baseline and follow-up measures. A final sample size of 56 per arm (224 total) was predicted to provide >80% power to detect adjusted effect sizes of ≥0.60 × SD between any two treatment groups in baseline-adjusted comparisons of either of the primary outcome measurements; the analysis plan specified a closed testing procedure in order to maintain a study-wide $\alpha = 0.05$ (see Appendix 4 in Supplementary Data). Anticipating 10% loss to follow-up, the enrollment target was initially 255; however, observed loss to follow-up as the study proceeded was slightly higher, so a total of 267 participants were randomized. Only individuals with complete data were included in these outcome analyses.

RESULTS

Participant Characteristics

Two hundred sixty-seven individuals were randomized (Supplementary Fig. 1). Table 1 presents baseline demographic and metabolic characteristics of randomized participants by treatment arm. The cohort had a mean ± SD age of 53.9 ± 8.9 years and BMI of 35.0 ± 5.7 kg/m^2. Diabetes was previously present (*n* = 5; median [range] duration 17 [4–129] days) or newly diagnosed during screening (*n* = 65) in 26% of the cohort; mean HbA_{1c} in the entire cohort at study entry was 39.3 ± 4.2 mmol/mol (5.75 ± 0.39%). There were no differences across treatment groups in race/ethnicity distribution, anthropometrics, blood pressure, lipids, or glycemia. There were disproportionately more women in the metformin-alone treatment group (*P* = 0.04) (Table 1).

Adherence to Interventions

Blinded tablet adherence, defined as the percent of total expected pills taken, ranged from 90% to 93% in the metformin arm and 92% to 94% in the placebo arm during quarterly visits over 12 months of treatment.

During weeks 11–12, the mean ± SD glargine dose in the G/M group was 0.34 ± 0.14 units/kg/day (range 0.11–0.77). Fasting plasma glucose decreased from a mean of 6.1 ± 0.6 mmol/L at baseline to a fasting self-monitored blood glucose mean of 5.2 ± 0.4 mmol/L at weeks 11–12, with 42% of participants achieving the 4.4–5.0 mmol/L goal (Fig. 1). For insulin treatment, 85% of participants were >80% adherent. In the G/M group, adherence

Table 1—Baseline physical and demographic characteristics by treatment group

	Glargine followed by metformin (n = 67)	Liraglutide with metformin (n = 68)	Metformin alone (n = 65)	Placebo (n = 67)	P value
Age at randomization (years)	53.5 ± 9.3	54.0 ± 8.1	55.2 ± 8.2	52.8 ± 10.0	0.49
Sex					0.04
Women	23 (34.3)	29 (42.6)	37 (56.9)	25 (37.3)	
Men	44 (65.7)	39 (57.4)	28 (43.1)	42 (62.7)	
Race/ethnicity					0.66
White	37 (55.2)	40 (58.8)	34 (52.3)	30 (44.8)	
Black	21 (31.3)	20 (29.4)	19 (29.2)	21 (31.3)	
Hispanic (any)	5 (7.5)	6 (8.8)	6 (9.2)	11 (16.4)	
All other	4 (6.0)	2 (2.9)	6 (9.2)	5 (7.5)	
Glycemic group					0.97
IGT	50 (74.6)	49 (72.1)	49 (75.4)	49 (73.1)	
Diabetes	17 (25.4)	19 (27.9)	16 (24.6)	18 (26.9)	
Weight (kg)	104.4 ± 20.0	104.2 ± 21.0	98.1 ± 18.6	101.6 ± 19.3	0.23
BMI (kg/m^2)	35.0 ± 5.9	35.6 ± 5.8	35.0 ± 5.1	34.4 ± 5.9	0.66
HbA_{1c} (mol/mmol)	39.9 ± 3.6	38.6 ± 4.3	39.5 ± 4.3	39.1 ± 4.7	0.32
HbA_{1c} (%)	5.80 ± 0.33	5.69 ± 0.39	5.77 ± 0.40	5.73 ± 0.43	0.32
Fasting glucose (mmol/L)	6.22 ± 0.74	6.11 ± 0.50	6.21 ± 0.67	6.08 ± 0.58	0.45
Fasting insulin (pmol/L)	112.8 [32.2, 394.6]	111.5 [37.3, 333.5]	104.5 [37.7, 289.2]	93.5 [31.2, 280.4]	0.16
Fasting C-peptide (nmol/L)	1.34 ± 0.69	1.25 ± 0.43	1.23 ± 0.42	1.16 ± 0.44	0.23
2-h glucose (mmol/L)	10.3 ± 2.4	9.9 ± 2.2	10.1 ± 2.4	10.1 ± 2.3	0.80
Systolic BP (mmHg)	127.7 ± 12.0	126.1 ± 13.3	127.1 ± 13.3	125.3 ± 14.6	0.74
Diastolic BP (mmHg)	78.7 ± 9.5	75.0 ± 9.3	77.8 ± 11.1	76.7 ± 11.4	0.19
Hypertensive					0.31
No	17 (25.4)	25 (36.8)	16 (24.6)	23 (34.3)	
Yes	50 (74.6)	43 (63.2)	49 (75.4)	44 (65.7)	
BP-lowering medication use					0.43
No	33 (49.3)	34 (50.0)	30 (46.2)	40 (59.7)	
Yes	34 (50.7)	34 (50.0)	35 (53.8)	27 (40.3)	
Total cholesterol (mmol/L)	4.21 ± 0.96	4.39 ± 0.91	4.51 ± 0.94	4.26 ± 0.98	0.27
LDL cholesterol (mmol/L)	2.41 ± 0.77	2.56 ± 0.81	2.68 ± 0.81	2.42 ± 0.79	0.15
HDL cholesterol (mmol/L)	1.12 ± 0.24	1.15 ± 0.25	1.17 ± 0.30	1.15 ± 0.33	0.76
Triglycerides (mmol/L)	1.36 [0.58, 3.20]	1.35 [0.58, 3.13]	1.28 [0.50, 3.28]	1.28 [0.45, 3.62]	0.93
Triglyeride/HDL ratio	1.09 ± 0.47	1.05 ± 0.52	0.93 ± 0.71	0.93 ± 0.72	0.35
Non-HDL cholesterol (mmol/L)	3.09 ± 0.92	3.23 ± 0.86	3.34 ± 0.90	3.11 ± 0.92	0.36
Lipid-lowering medication use					0.32
No	36 (53.7)	41 (60.3)	45 (69.2)	39 (58.2)	
Yes	31 (46.3)	27 (39.7)	20 (30.8)	28 (41.8)	

Data are presented as n (%), mean ± SD for normally distributed variables, or geometric mean [95% CI] for nonnormally distributed variables. P values reflect a one-way ANOVA comparing continuous variables across groups or a χ^2 test comparing distributions of categorical variables across groups. BP, blood pressure.

to open-label metformin ranged from 91% to 92% over time.

Liraglutide adherence was 92%, with 67% of participants on the 1.8 mg/day dose through 12 months of therapy. Four participants were unable to tolerate liraglutide, resulting in three completely withdrawing from the study before month 3 and the fourth after month 9. In the L+M group, adherence to open-label metformin ranged from 91% to 92%.

Study withdrawals principally occurred between baseline and M12, with lowest loss to follow-up in the G/M group and greatest in the L+M group and others intermediate. The numbers of participants studied at M12 and M15 were nearly identical in each intervention arm (Supplementary Fig. 1).

Treatment Effects on Insulin Sensitivity, β-Cell Responses, and β-Cell Function

Figure 2 presents hyperglycemic clamp data from baseline, M12, and M15. Clamp glucose targets were achieved in all randomized treatment groups at every time point. At M12, the L+M group had significantly higher C-peptide concentrations at all time points during the hyperglycemic clamp ($P < 0.01$). Supplementary Table 1 presents the derived β-cell response and insulin sensitivity measures across the three time points.

Figure 3 presents the trajectories of treatment-induced change in β-cell function within each treatment group, showing β-cell responses in relation to insulin sensitivity. The black line represents the baseline relationship in the whole cohort. Movement above the line represents improvement and below the line deterioration in β-cell function, whereas movement along the line represents mutually concordant changes in sensitivity

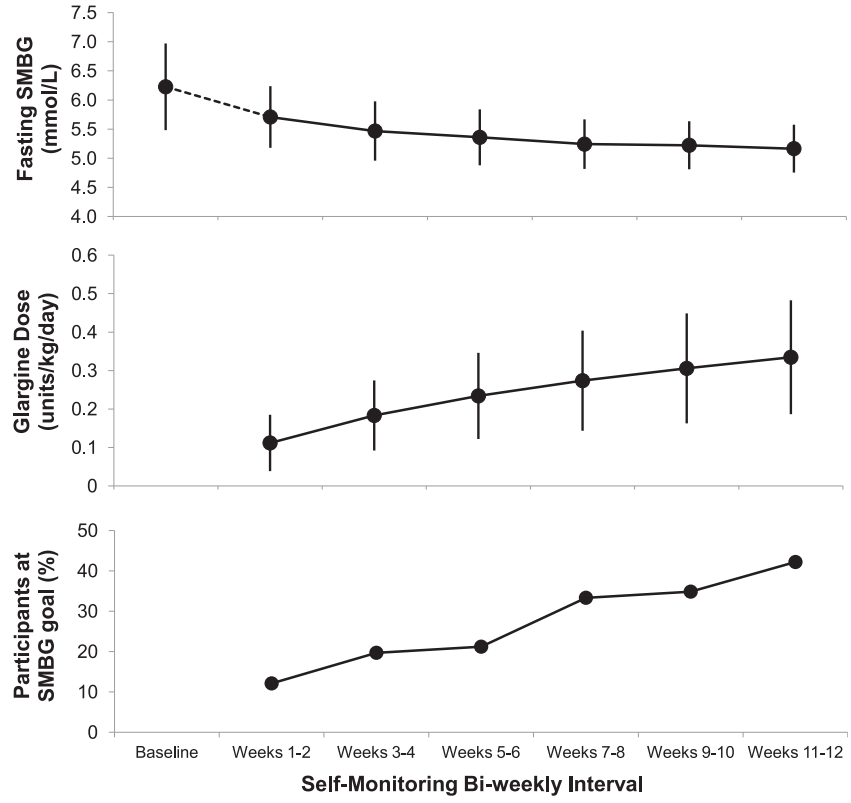

Figure 1—Insulin doses and corresponding fasting glucose values over time while on glargine treatment. Mean fasting morning self-monitoring of blood glucose (SMBG) value over 12 weeks of glargine treatment (top panel), mean insulin dose expressed in units/kg multiplied by 100 corresponding to each time point (middle), and corresponding percentage of participants every 2 weeks that achieved the goal fasting SMBG of 4.4–5.0 mmol/L (bottom). The baseline glucose concentration was a laboratory-based measurement prior to initiation of insulin and SMBG. Data are displayed as mean and 95% CI.

and response without a change in underlying β-cell function.

M15 Compared With Baseline

The primary analysis compared responses at M15, jointly evaluating β-cell response and insulin sensitivity. Insulin sensitivity, determined as M/I, improved from baseline to M15 in the metformin (P = 0.027) and G/M (P = 0.018) groups and was unchanged in the other groups. While the placebo group exhibited no difference in the joint values of SSCP and insulin sensitivity at M15 compared with baseline (P = 0.14), the three active treatment groups showed concordant changes in SSCP and insulin sensitivity, reflecting a decrease in secretion response compared with baseline (metformin, P = 0.031; G/M, P = 0.002; L+M, P = 0.018) (Fig. 3, upper panel). These measures were not different among treatment groups at M15 (P = 0.84). Because decreases in SSCP were proportional to increases in insulin sensitivity (i.e., not different from the regression line), they represent no change in β-cell function at M15 compared with baseline.

At M15, the joint change of $ACPR_{max}$ and insulin sensitivity indicated a reduced secretion response compared with baseline in the metformin (P = 0.025), G/M (P = 0.002) and placebo (P = 0.050) groups but not different from baseline in the L+M group (P = 0.083) (Fig. 3, middle panel). These changes were not statistically different across the four treatment groups (P = 0.81) and they were modest in magnitude, such that overall $ACPR_{max}$ paired with insulin sensitivity at M15 did not deviate from the line representing baseline β-cell function except in the placebo group, which fell below the line.

At M15, the joint change in $ACPR_g$ with insulin sensitivity was different from baseline only in the G/M group (P = 0.013), reflecting modestly reduced $ACPR_g$ in this group (Fig. 3, lower panel). Overall, however, there was no significant difference in $ACPR_g$ paired with insulin sensitivity among groups at M15 (P = 0.81) and no evidence of a shift away from the underlying line relating the C-peptide response with insulin sensitivity for any group.

Thus, overall, there was a small increase in insulin sensitivity along with modest declines in β-cell responses at M15 compared with baseline, but the changes were not statistically different among treatment groups and represented no change in underlying β-cell function at M15 compared with the baseline curve.

M12 Compared With Baseline

These neutral effects at M15 occurred despite significant and importantly different on-treatment effects at M12. At that time, insulin sensitivity was unchanged compared with baseline in the G/M (P = 0.18) and placebo (P = 0.90) groups but significantly increased in the metformin group (P = 0.0002). In the L+M group, the calculated M value doubled (0.021 vs. 0.046 mmol/kg/min), but the achieved steady-state insulin concentrations were magnified to a greater extent, resulting in a numerically lower M/I value (2.92×10^{-5} vs. 2.33×10^{-5} mmol/kg/min per pmol/L) that was not statistically different from baseline (P = 0.060).

A modest change from baseline in the joint measure of SSCP with insulin sensitivity was seen at M12 in the metformin (P = 0.0007) and placebo (P = 0.034) groups, moving along the baseline curve relating SSCP with insulin sensitivity. A much larger increase was seen in the L+M group ($P < 0.0001$), reflecting an increase in SSCP. There was no change in this aspect of β-cell function at M12 in the G/M group (P = 0.24) (Fig. 3, upper panel). These changes differed significantly across the four groups ($P < 0.0001$), with greater effects in L+M versus each of the other three groups and without significant differences among the other treatment groups. Comparing them against the curve representing the baseline relationships between the secretory response and insulin sensitivity, only the changes in the L+M group represent improved β-cell function at M12 compared with baseline.

At M12 in the L+M group, the joint change in arginine-stimulated incremental C-peptide response with insulin sensitivity was diminished compared with

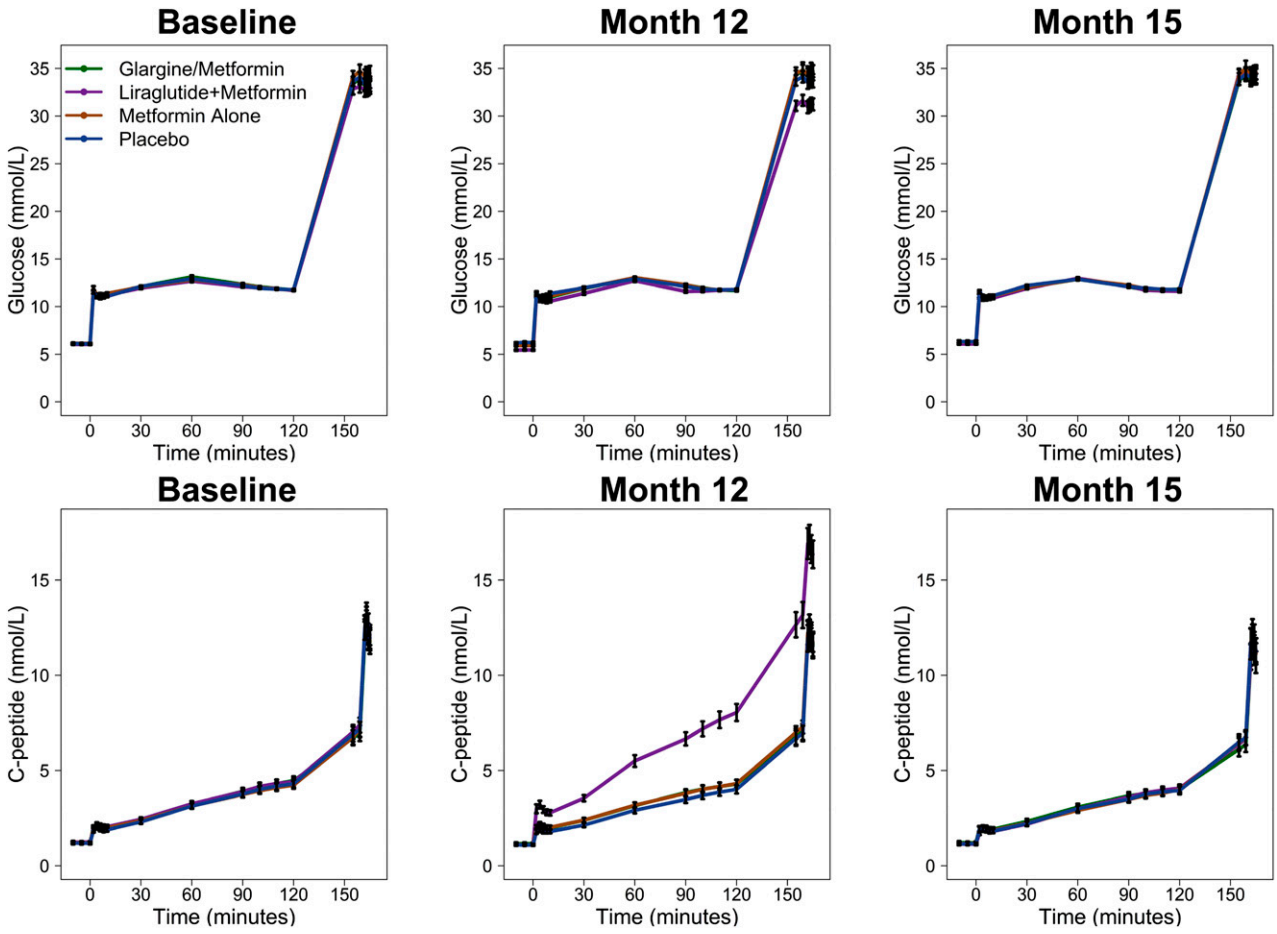

Figure 2—Glucose and C-peptide concentrations during the hyperglycemic clamp. Glucose and C-peptide values from the hyperglycemic clamps at baseline, after 12 months of treatment (Month 12), and 3 months after discontinuing the intervention (Month 15). The goal steady-state glucose targets were 11.1 mmol/L between 90 and 120 min and >25 mmol/L at 150 min. Data are displayed as mean ± SEM.

baseline ($P < 0.001$). The C-peptide concentrations achieved immediately prior to arginine administration were greater than those seen with the other treatments (Fig. 2) ($P < 0.001$); from this starting point, the arginine-stimulated increment was lower in those treated with L+M ($P = 0.019$). In the metformin group, a more modest reduction was seen in the joint change in $ACPR_{max}$ and M/I ($P = 0.0002$) due to increased insulin sensitivity with a small proportional decrease in $ACPR_{max}$; this joint change was not different from baseline in the G/M or placebo groups ($P = 0.29$ and $P = 0.17$, respectively). The four-group comparison revealed a highly statistically significant difference in $ACPR_{max}$ jointly with insulin sensitivity among the groups ($P < 0.0001$), with the L+M group diminished relative to others and without statistical differences among the other three treatments. The changes in the L+M group represent a reduction in this aspect of β-cell function at M12 compared with baseline.

For $ACPR_g$ at M12, the joint change from baseline in $ACPR_g$ with insulin sensitivity was significant in all three active treatment groups (metformin, $P = 0.0002$; G/M, $P = 0.048$; L+M, $P < 0.0001$) but not in the placebo group ($P = 0.98$). In the active treatment groups, increases in both $ACPR_g$ and insulin sensitivity produced a shift above baseline (Fig. 3, lower panel). The four-group comparison was statistically significant ($P < 0.0001$), again due to significant pairwise differences when the L+M group was compared against the other treatment arms. The changes in the L+M group, and to a lesser extent in the metformin and G/M groups, represent improvement in this aspect of β-cell function at M12 compared with baseline.

Parallel analyses were performed in the subgroup of participants with IGT at baseline (74% of the total cohort). The overall pattern, magnitude, and statistical significance of the results in the IGT subgroup were similar to those seen in the full cohort (Supplementary Fig. 2).

Temporal Patterns of BMI and Glycemia

Randomized treatments were associated with different patterns of change in BMI and glycemia (Fig. 4). At M12, BMI fell in all three active intervention groups ($P < 0.0001$) compared with baseline, but it did not change in the placebo group. Following withdrawal of therapy, BMI increased in the three intervention groups but remained lower than baseline (each $P < 0.05$).

HbA_{1c} at M12 was significantly lower than baseline in the G/M group ($P < 0.05$) and lowest in the L+M group ($P < 0.0001$) (Fig. 4). At M15, HbA_{1c} in the active treatment groups was at or above baseline. HbA_{1c} was stable across the full 15 months in the placebo group.

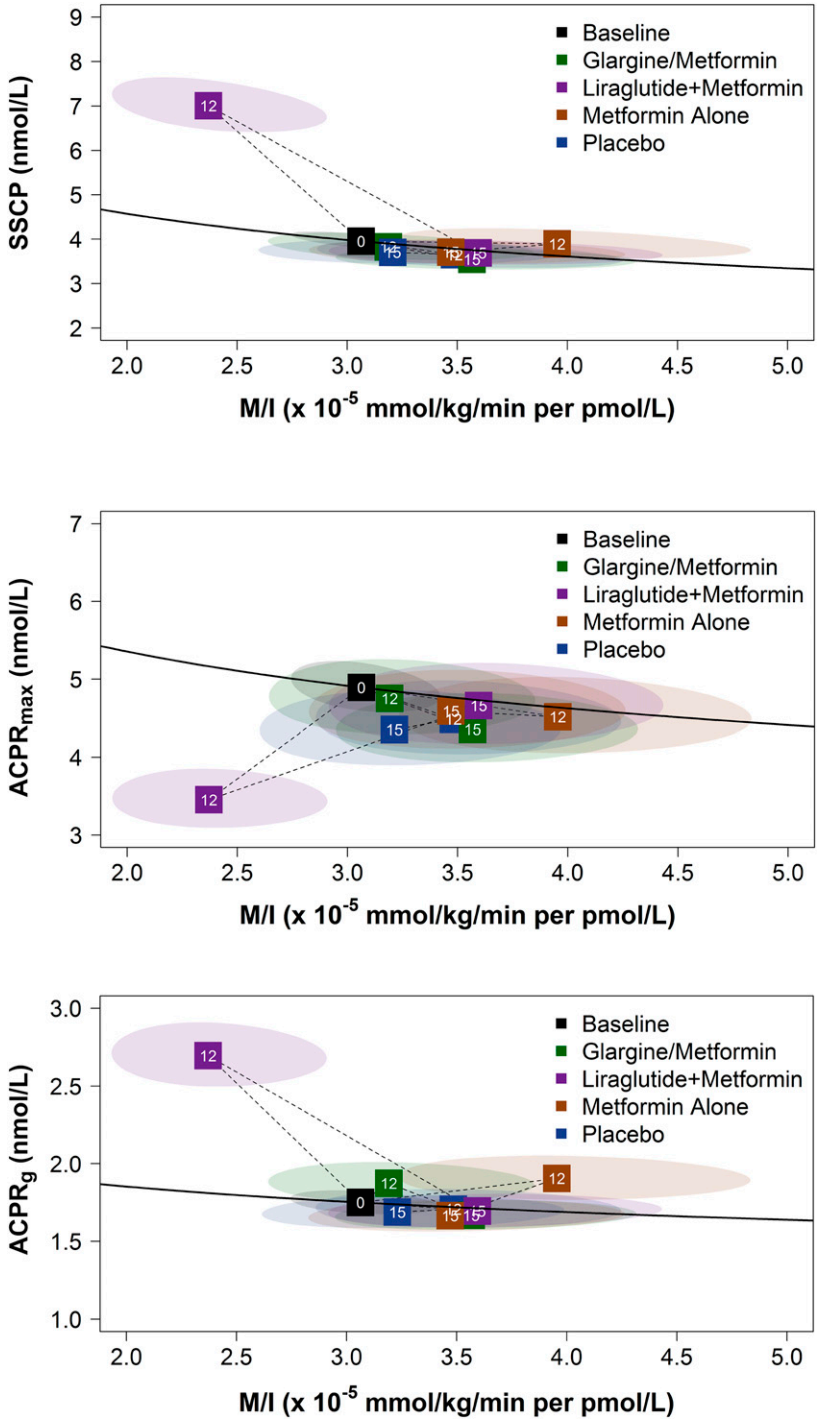

Figure 3—Vector plots demonstrating the effects of study interventions on β-cell function: co–primary outcomes (SSCP and $ACPR_{max}$) and a secondary outcome ($ACPR_g$) paired with insulin sensitivity (M/I). Model-based changes over time from baseline to 12 and 15 months for the clamp-derived measures of insulin responses (SSCP, $ACPR_{max}$, and $ACPR_g$), each plotted with insulin sensitivity quantified as M/I. The black line depicts the joint relationship between each β-cell response and insulin sensitivity at baseline for the full cohort, with the mean value at baseline for the full cohort indicated by the black box with 0 inside. The dotted lines to boxes at values for months 12 and 15 show the trajectory of values from baseline to month 12 of intervention and then to month 15 (3 months following discontinuation of the intervention). Groups are presented as metformin alone in brown, G/M in green, L+M in purple, and placebo in blue. The ellipses depict the 95% confidence bands around the points at months 12 and 15; where these ellipses overlap the solid black line, the value is not statistically different from the baseline. Values above the black line represent improved β-cell function and values below the line represent worsened β-cell function. See RESULTS for within-group and between-group comparisons at each time point.

Safety Outcomes

Serious adverse events occurred in 17 individuals. None was deemed related to randomized study medications or study procedures. These and other nonsevere, targeted adverse events are summarized in Supplementary Table 2. No participants had protocol-defined severe hypoglycemia or acute metabolic decompensation.

One participant was treated with an intra-articular steroid injection before M12 that provoked an unrecoverable worsening of glycemia requiring out-of-study diabetes management. This participant did not contribute M15 data for the current analyses.

CONCLUSIONS

The RISE Adult Medication Study tested interventions to preserve or improve β-cell function in individuals with IGT or early type 2 diabetes, evaluating persistence of treatment-induced changes after a 3-month period of treatment withdrawal. At the end of 12 months of treatment, there were significant increases in glucose-stimulated β-cell responses, which were greatest in the L+M group. The arginine-stimulated response was unexpectedly lower at M12 in the L+M group. All on-treatment effects disappeared 3 months after treatment was stopped, arguing against an ongoing effect of any of the tested treatment approaches to alter underlying β-cell function.

Data from preclinical models suggest that GLP-1 mimetics can protect and augment β-cell function (32,33), with some caveats (34). Three studies in humans have undertaken similar tests of persisting benefit of GLP-1 agonists following treatment withdrawal. Bunck and colleagues (14,15) studied a cohort with short-duration type 2 diabetes and showed beneficial effects of exenatide on glucose-stimulated β-cell responses at 1 year and 3 years on treatment (with significant dropouts between 1 and 3 years). However, when treatment was stopped for 4 weeks at the end of the first year, β-cell responses returned to baseline (14). After 3 years of treatment, an equivocally persistent benefit was reported following 4-week treatment withdrawal in the subset of the cohort treated for this duration (15). Retnakaran et al. (16) subsequently published a study in individuals with

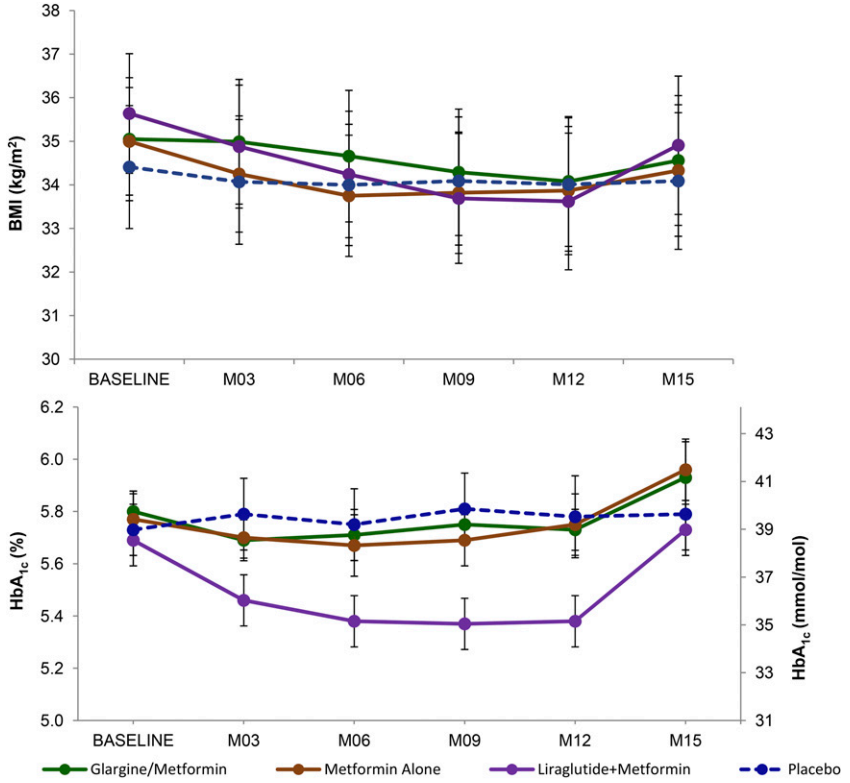

Figure 4—BMI and HbA_{1c} across the 15 months of observation. Data are displayed as mean ± SEM.

type 2 diabetes for an average duration of 2.6 years and found beneficial effects on β-cell function after 48 weeks of liraglutide; however, these benefits were entirely lost 2 weeks after treatment withdrawal. A larger dose of liraglutide given for a longer interval (3.0 mg daily for up to 3 years) was compared against placebo for weight loss in a population earlier in the spectrum of dysglycemia than the RISE cohort and was also used to evaluate protection from progression to diabetes (35). At the end of 3 years of treatment, diabetes protection was seen coincident with persisting weight loss differences between groups. Following 3 months' treatment withdrawal, with partial weight regain there was mitigation of the diabetes protection effect. Effects on β-cell function following treatment withdrawal were not reported (35). In RISE, the large on-treatment effects of liraglutide in subjects with IGT and recently diagnosed type 2 diabetes disappeared entirely when assessed 3 months after treatment withdrawal, at which time most of the weight benefit from liraglutide had disappeared. Collectively, these studies argue that beneficial effects of GLP-1 agonists on β-cell function are likely limited to the period of treatment and do not persist following treatment withdrawal.

There was a lower arginine-stimulated increment in the C-peptide response in the L+M group at the M12 (on-treatment) time point compared with baseline. This is in the setting of significantly elevated total C-peptide concentrations prior to arginine administration but nevertheless represents a reduction in the stimulated response. In the Bunck et al. study (14), exenatide treatment resulted in a marked increase in C-peptide release during glucose infusion but no change in the incremental response to arginine when measured under 15 mmol/L glucose conditions. These observations suggest that GLP-1 agonist effects on β-cell function are specific to glucose-stimulated responses; alternatively, there could be a ceiling for the maximal response in this population. Understanding this phenomenon will require additional investigation in humans, perhaps including comparisons of oral and intravenous glucose loads.

In RISE, persistent benefits of treatment were not seen with insulin glargine followed by metformin after treatment withdrawal. This is in contrast to studies in individuals with diabetes and prediabetes that have shown durable benefits following treatment discontinuation using insulin-based approaches. In studies from China, among individuals with newly diagnosed type 2 diabetes (HbA_{1c} 9.5–9.8%), aggressive treatment with basal/bolus insulin injections or insulin by pump for as little as 2 weeks resulted in sustained diabetes remission, tied to improved β-cell function (11,12). In the Outcome Reduction With Initial Glargine Intervention (ORIGIN) study, among individuals without diabetes at baseline, prior treatment with glargine for over 6 years reduced subsequent diabetes development assessed 3 months after study treatments were stopped (36). Other studies are consistent with the present observations, including a 24-month pilot study of intermittent insulin treatment to delay progressive glycemic worsening in short-duration type 2 diabetes (37) and the glargine treatment arm of the study by Bunck and colleagues (14,15). The differences across studies in these results may simply reflect different measurement end points (glycemia versus β-cell function measures), but they may also reflect differences in the treated populations (glycemic status, magnitude of glucose toxicity, racial/ethnic differences), concurrent changes in diet or lifestyle, and timing and pattern of insulin exposure (i.e., basal versus basal/bolus exposure). Overall, these observations suggest that 3 months of glargine followed by 9 months of metformin does not impact the progressive β-cell dysfunction that underlies glycemic worsening in prediabetes and early type 2 diabetes.

Beneficial on-treatment effects of metformin on β-cell function had dissipated after 3 months' withdrawal. At M15, modest residual changes in insulin sensitivity were balanced by reductions in β-cell responses compared with baseline, indicating no net change in β-cell function compared with baseline. This finding extends observations from the DPP and its Outcome Study (DPPOS) (17,38), which have shown persisting long-term benefits from ongoing metformin treatment with regard to diabetes prevention. After ~3 years exposure to metformin in the DPP, repeat OGTT testing was performed after an average of 11 days of withdrawal of metformin

(24). At this early time point, about 26% of the glycemic benefit was lost. The RISE data provide observations of a more extended withdrawal in a broadly comparable cohort and argue against an effect of metformin to alter the underlying progression of β-cell failure, despite improvements in metabolic physiology (4,5).

RISE did not study every available class of medication. In particular, thiazolidinediones have been convincingly shown to exert durable diabetes prevention effects with improvement in β-cell function (9,20,21). Notably, 1 year after withdrawal of pioglitazone therapy in the Actos Now for Prevention of Diabetes (ACT NOW) study the beneficial effects on β-cell responses had dissipated (22), although a net diabetes prevention effect persisted. Newer glucose-lowering drug classes, such as the sodium–glucose cotransporter 2 inhibitors, have not been evaluated for diabetes prevention, but the newly recognized actions on α-cells to drive glucagon production (39) do not augur well for a beneficial effect on β-cells. In aggregate, the current observations plus the outcomes of other attempts to reverse declines in β-cell function argue against further tests of strategies that include withdrawal of treatment in populations at risk for diabetes or with established diabetes. Of course, lack of efficacy following treatment withdrawal does not imply lack of efficacy during active treatment, and in fact the current data demonstrate on-treatment benefits that can be used to inform the design of future studies. Also, a separate RISE protocol compared gastric band surgery to metformin and suggested that an additional 9 kg of weight loss with surgery in IGT or early type 2 diabetes is not superior to ongoing metformin alone (40). Greater degrees of weight loss with alternative forms of surgery may have a greater beneficial effect on β-cell function and diabetes prevention, but this has not yet been examined in a study designed primarily for that purpose.

This study has a number of strengths, including a randomized study design, inclusion of placebo treatment and metformin treatment arms, and a robust, multicenter approach to quantification of insulin sensitivity and β-cell responses to glucose and to arginine. By quantifying insulin sensitivity and β-cell responses simultaneously, we were able to account for the well-recognized interrelationship of these factors and to provide mechanistic insight into the impact of the interventions on β-cell function over time. The principal limitation of this study was that target fasting glycemia was achieved in only 42% of the glargine-treated individuals, although glargine adherence was good and fasting glucose values were reduced by ~0.5 mmol/L. Also, more participants in the L+M group did not complete the study, although this was unlikely to have confounded the observed outcome as this group experienced the largest on-treatment effects. The use of glucose clamps for study end points limits the direct clinical interpretability of these results.

In conclusion, the RISE Adult Medication Study has shown clinically important effects of the study medications, especially the combination of liraglutide with metformin, to alter β-cell function while on treatment but without persisting efficacy following withdrawal of the interventions. These observations argue that currently available strategies targeting restoration or preservation of β-cell function in prediabetes require ongoing exposure to active interventions.

Appendix

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Author Contributions. The steering committee (principal investigator at each site, the data coordinating center, and the NIDDK project scientist) designed and implemented the study. All writing group members performed the research. S.L.E. performed all data analysis. K.J.M. wrote the first draft. D.A.E., S.E.K., S.L.E., S.A.A., T.A.B., S.C., E.W.L., and K.J.N. contributed to the discussion and edited the manuscript. K.J.M., S.E.K., and S.L.E. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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